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REVIEW ARTICLE

Sustainable approaches in aquaculture: Pharmacological and natural alternatives to antibiotics

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ABSTRACT

Aquaculture, a vital component of global food production, faces challenges such as antimicrobial residues and resistance due to the extensive use of antibiotics. This review explores sustainable alternatives to antibiotics in aquaculture. Vaccines play a critical role in disease prevention, significantly reducing antibiotic reliance. Phage therapy targets specific bacterial pathogens, offering an environmentally friendly solution, while quorum quenching disrupts bacterial communication, reducing virulence without promoting resistance. Probiotics and prebiotics enhance gut health and disease resistance, with synbiotics showing synergistic effects. Emerging technologies such as parabiotics and postbiotics, along with advances in metagenomics and next-generation sequencing, improve our understanding of microbiomes, leading to more effective disease control strategies. Medicinal plants provide cost-effective, natural antimicrobial and immune-stimulating properties, while nanoparticles degrade antibiotics, reducing pollution. A multifaceted approach that integrates these methods can mitigate antimicrobial resistance risks, ensuring the sustainability of aquaculture. Tailoring strategies to specific environmental conditions, species, and pathogens is crucial, emphasizing the need for continuous development and adaptation to maintain the long-term viability of the aquaculture industry.

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Introduction

Aquaculture involves growing aquatic organisms for food in various environments such as freshwater, saltwater, and brackish water. This industry operates in diverse locations, from coastal and riverside areas to land-based systems, and in a range of climates from tropical to temperate. Aquaculture encompasses a wide biodiversity, including seaweeds, mollusks, crustaceans, and various species of fish. Production methods fall into three main categories: extensive (low intensity with natural nutrition), semi-intensive, and intensive (high intensity with artificial nutrition). The use of technologies to manage aquaculture varies based on economy, infrastructure, and species being cultured. Consequently, aquaculture ranges from high-tech international farming of valuable species to low-tech agriculture (Kumar et al., 2018; Bondad-Reantaso et al., 2023). Since the 1980s, aquaculture has expanded rapidly to satisfy rising production demands. According to the FAO, global fisheries and aquaculture production reached a new record high of 214 million tonnes in 2022, driven largely by the growth in aquaculture, which accounted for 46% of the total production. This upward trend is expected to continue, with projections suggesting a 15% increase in global fish production by 2030, reaching approximately 245 million tonnes (FAO, 2023). However, this rapid expansion and globalization have brought challenges, such as the emergence and spread of diseases, necessitating the use of antimicrobials to improve production (Cabello et al., 2013; Schar et al., 2020). New reports indicate that pathogenic agents have undergone changes, reducing the effectiveness of common antimicrobials. Consequently, the doses of antimicrobials used in fish have been increasing over the years to maintain their efficacy (Erkinharju et al., 2021; Duman et al., 2023).

Aquatic organisms can harbor various potentially pathogenic microorganisms. The presence and impact of these pathogens are influenced by factors specific to the host, the pathogen itself, and the environment. Antibiotics frequently used in aquaculture typically target Gram-negative bacteria, as the most common pathogens in this field are usually aerobic, Gram-negative rods (Schar et al., 2020; Petty et al., 2022; Hossain et al., 2022). According to a 2012 study by the Food and Agriculture Organization of the United Nations (FAO), the most used antibiotics in farms are oxytetracycline, florfenicol, and trimethoprim/sulfadiazine (Alday-Sanz et al., 2005). However, the use of antibiotics differs significantly between regions and countries. In developed regions such as Europe, North America, and Japan, antibiotic use is tightly regulated, resulting in lower usage, particularly in countries like Norway and Scotland where the amount of antibiotics used per harvested salmon is minimal. Conversely, in countries like China, Vietnam, Thailand, and Chile, antibiotic use is considerably higher, leading to widespread antimicrobial resistance in pathogens such as *Aeromonas*, *Vibrio*, and *Acinetobacter* species. For instance, China alone uses an estimated 15,000 to 20,000 tons of antibiotics annually, while Thailand's shrimp farming consumes around 600 metric tons, both contributing to significant resistance rates (Preena et al., 2020; Deekshit et al., 2023). Metaphylactic use of antibiotics, treating the entire population rather than individual animals, is generally preferred (Cabello et al., 2013).

Exposure to antibiotics at subtherapeutic levels can lead to the development of resistant mutants. Once resistance develops in a bacterial strain, it can spread to other species and strains via gene transfer (Nesse & Simm, 2018). As a result, managing common bacterial diseases in aquaculture, such as furunculosis and edwardsiellosis, is becoming increasingly challenging due to the rise in antimicrobial resistance (AMR) (WHO, 2006). Although minimized levels of antibiotics in aquaculture environments can originate from human wastewater, most are directly used in aquaculture (Santos & Ramos, 2018). Technologies are being developed to remove these molecules in wastewater treatment before they are released into the environment (Salgueiro et al., 2020; Bondad-Reantaso et al., 2023).

Antimicrobial residues in food and animal products present significant socio-economic and public health challenges. Key health effects include the development of AMR, disruption of normal intestinal flora, allergies, anaphylactic shock, nephropathy, bone marrow depression, carcinogenicity, teratogenicity, and mutagenicity (Arsène et al., 2022). The indiscriminate use of antimicrobials contributes to these residues and their adverse health impacts. Therefore, control measures are necessary to reduce antibiotic use and protect consumers (Okocha et al., 2018).

According to the FAO/OIE/WHO expert consultation on aquaculture held in Seoul, South Korea, from June 13-16, 2006, the hazards of antimicrobial use are summarised as antimicrobial residues and antimicrobial resistance (AMR) (WHO, 2006). The report concludes that AMR is a more serious problem because it transcends phylogenetic and geographic boundaries, can spread among aquatic bacteria and animal and human pathogens. For example, resistance to aquatic animal pathogens can render fish disease treatments ineffective and may be transferred to animal and human pathogens, complicating treatment. Another issue with antimicrobial use in aquaculture is that treatment is usually administered through feed, unlike in terrestrial environments. This method can affect the efficiency of treatment by reducing the feed intake of sick animals, and unused feed with medication may remain in sediments, where resistant bacteria can be selected, increasing the resistance pool in the aquatic environment. Therefore, finding alternatives to antibiotic use is vital for the sustainability of the sector (Bondad-Reantaso et al., 2023).

Antibiotic residues in aquaculture products are one of the most common reasons for product returns in major fish markets such as the European Union (EU), the United States (US), and Japan. This situation often results in the destruction of products and significant economic losses for exporting countries. In most aquaculture-producing countries, residue monitoring is conducted according to international market requirements. Many countries strive to comply with EU standards, particularly since the EU is a major importer of seafood. The EU uses the most sensitive detection methods for chemicals banned in aquaculture. However, differences in permitted aquaculture pesticides and maximum residue limits exist among producing countries (Karunasagar, 2020).

The spread of AMR can occur in aquatic environments, such as wastewater from hospitals and farms, through irrigation water, or through its use in animal farms. Wild animals and birds traveling long distances can also carry resistant bacteria to different environments. Therefore, combating antimicrobial resistance requires considering both aquaculture and environmental factors (Zeballos-Gross et al., 2021). Controlling the use of antibiotics in aquaculture not only helps reduce global antibiotic resistance, but also includes alternative strategies, such as strengthening the immunity of aquatic organisms and reducing the virulence (FAO, 2019).

The aim of this review is to examine the scope of problems related to antimicrobial use and the importance of AMR in aquaculture, review the existing literature, evaluate antibiotic use and alternative treatment methods such as vaccination, bacteriophages, bacteriocins, use of probiotics and prebiotics, quorum quenching, chicken egg yolk antibody, nanoparticles, recombinant proteins, and medicinal plant derivatives.

Antibiotics in Aquaculture

Aquaculture faces significant challenges due to disease outbreaks often caused by poor environmental conditions, such as improper farm management and malnutrition. This leads to secondary bacterial infections that require antibiotics for therapeutic, preventive, and metaphylactic purposes (Cabello et al., 2013). Common antibiotics include tetracycline, oxytetracycline, oxolinic acid, amoxicillin, flumequine, sarafloxacin, enrofloxacin, erythromycin, sulfadimethoxine, ormethoprim, and florfenicol (FAO, 2019).

Most antibiotics used in aquaculture enter the environment intact, causing horizontal gene transfer due to residues in polluted water, biofilms, and bacteriophages (Watts et al., 2017). These residues pose post-treatment risks (Cabello et al., 2013). The use in ornamental fish can lead to resistant bacterial strains and facilitate their global spread (Watts et al., 2017).

Tetracyclines, such as oxytetracycline, are widely used in countries like the United States and Norway due to their broad-spectrum activity and affordability. However, overuse has led to significant resistance issues (Grossman, 2016). In Norway, the usage of antibiotics is tightly controlled, and the amount used per ton of harvested fish is less than 1 gram, largely due to effective vaccination programs and stringent regulations (Sommerset et al., 2005). In contrast, Chile has reported higher usage, with up to 500 grams of antibiotics per ton of harvested salmon, contributing to the emergence of resistant strains of *Piscirickettsia salmonis* (Cabello et al., 2013). This high usage rate reflects the reliance on antibiotics in the absence of similarly stringent regulations and effective alternative disease management strategies. In Türkiye, antibiotics like oxytetracycline and florfenicol are commonly used in aquaculture. The use of oxytetracycline is widespread due to its cost-effectiveness and broad-spectrum activity, but there are concerns about increasing resistance, especially among Vibrio and Aeromonas species (Duman et al., 2023). European Union countries, including Scotland, have strict regulations on antibiotic use in aquaculture, favoring vaccination and other preventive measures. For example, the use of quinolones and fluoroquinolones is heavily restricted and generally reserved for human medicine to avoid cross-resistance issues (Bondad-Reantaso et al., 2023). In Vietnam, high levels of antibiotic use in aquaculture have been linked to the development of multi-drug resistant Aeromonas species, posing significant challenges for disease management (Lulijwa et al., 2020). The country continues to struggle with implementing effective regulations to control antibiotic use in aquaculture. Nitrofurans, such as furazolidone, are banned in many countries due to their carcinogenic risks, yet they have been historically used in some regions where regulatory oversight is less stringent (Antunes et al., 2006). Similarly, the use of rifampicin in aquaculture is limited due to resistance issues and potential impacts on human health (Lulijwa et al., 2020).

Alternatives to Antibiotics

In recent years, the rapid expansion of the industry has led to increased disease outbreaks, challenging the sustainability of production. The misuse of antimicrobial agents, leading to antibiotic-resistant genes (ARGs), has prompted the exploration of alternatives (Dowling et al., 2013; Bondad-Reantaso et al., 2023).

Vaccinations

Vaccines made from weakened or inactivated pathogens, are crucial for reducing fish diseases and antibiotic use in aquaculture. In Norwegian salmon farming, annual antibiotic use dropped from 50,000 kg in 1987 to less than 2,000 kg in 1997 due to vaccination strategies (Sommerset et al., 2005; Rodger, 2016).

Fish vaccination began in 1942 with a vaccine for *Aeromonas salmonicida* in *Oncorhynchus clarkii* trout. Advances in biotechnology and immunology have since led to many vaccines that combat bacterial and viral diseases in aquaculture (Adams, 2019). Most vaccines use inactivated microorganisms administered by immersion or injection (Ma et al., 2019). Whole-cell killed vaccines effectively target extracellular bacteria, while intracellular bacteria require vaccines that stimulate a cellular immune response (Munang'andu, 2018).

A stronger antibody response can be achieved by using live vaccines. Due to their ability to proliferate or enter the host, these vaccines are administered orally or by immersion, providing both innate and adaptive immunity (Ma et al., 2019). Modified live vaccines are prepared from viruses or bacteria with attenuated virulence. They are obtained through chemical or physical processes, culture under abnormal conditions, or natural low virulence against target species (Adams, 2019). Molecular manipulations that lack virulence are also used to create weakening vaccines. This approach is useful for DNA viruses such as herpesviruses, as well as *Streptococcus spp.* and *Edwardsiella spp.* (Ma et al., 2019).

Injectable vaccines containing adjuvants and multiple antigens to protect against different diseases are used in commercial farms, particularly in Atlantic salmon (*Salmo salar*) (Sommerset et al., 2005). Furthermore, autogenous vaccines offer flexibility in cost and production, faster distribution, and the possibility of application during outbreaks (Adams, 2019).

Modern technological approaches to vaccine production, such as targeting specific pathogen components, recombinant technology, or DNA/RNA particle vaccines, are also believed to produce higher immunity. These vaccines use only antigenic components, eliminating replication risks in the host or environment (Hansson et al., 2000). Immunogenic components can be isolated from the pathogen or produced using specific proteins. *Escherichia coli* expression vectors have been used in Norway to combat infectious pancreatic necrosis (IPN) in salmonids by generating plasmids with protective antigen genes (Ma et al., 2019). These vaccines can be freeze-dried, but they are costly due to the need for effective adjuvants and multiple booster shots, leading to a weaker immune response (Adams, 2019).

Virus-like particles (VLPs) are advanced subunit vaccines formed by viral capsid proteins that mimic viruses without genomic material, preventing replication. They enhance immune responses and have shown experimental effectiveness against certain diseases (Noad & Roy, 2003).

Recently, nucleic acid vaccines for aquaculture have been developed that provide strong cellular and humoral immunity. DNA and RNA vaccines are easy to produce, safe, and cost-effective (Ma et al., 2019). DNA vaccines, made in bacterial cells with expression plasmids, offer cross-protection (Adams, 2019). A DNA vaccine for infectious hematopoietic necrosis virus (IHNV) is licensed in Canada. RNA-based vaccines, including non-amplifying and self-amplifying mRNA, show promise for human and animal use (Pardi et al., 2018).

In terms of country-specific regulations, several vaccines are allowed and widely used in aquaculture. In Norway, vaccines against infectious pancreatic necrosis (IPN) and salmonid alphavirus (SAV) are extensively utilized in Atlantic salmon farming (Erkinharju et al., 2021). Canada has licensed a DNA vaccine for infectious hematopoietic necrosis virus (IHNV), which is applied to various salmonid species (Adams, 2019). In the European Union, vaccines against *Aeromonas salmonicida* and *Yersinia ruckeri* are commonly used in trout farming to prevent furunculosis and enteric redmouth disease, respectively (Bondad-Reantaso et al., 2023). The United States employs vaccines for *Streptococcus iniae* and *Vibrio* spp. in tilapia and catfish aquaculture (Ma et al., 2019). In Japan, vaccines for *Edwardsiella tarda* and *Vibrio anguillarum* are used in yellowtail (*Seriola quinqueradiata*) and other marine species (FAO, 2020). Türkiye uses vaccines against *Lactococcus* *garvieae* and *Yersinia ruckeri* in rainbow trout (*Oncorhynchus mykiss*) farming to combat streptococcosis and enteric redmouth disease (Duman et al., 2023).

Bacteriophages

Bacteriophages are viruses that infect and lyse bacterial cells, particularly lytic phages that disrupt bacterial metabolism. Discovered in the early 1900s, they were initially considered a solution for bacterial diseases, but interest declined with the advent of antibiotics. However, with increasing antibiotic resistance, phage therapy is gaining attention. Phages are the most abundant microorganisms on Earth, especially in marine and freshwater environments, where they can survive for several weeks to over 5 to 7 months (Silva et al., 2014). Generally, phage survival is not affected by pH, salinity, temperature, or organic matter. Bacteriophages can integrate into host DNA as prophages or exist as replicons, as seen with *Vibrio* spp. (Choudhury et al., 2016). Phage therapy has been used to control bacterial infections successfully, with multiple phage therapy proving more effective than single treatments. Reports highlight the use of phage therapy against the Vibrionaceae family. Phages can control the most destructive bacteria, such as *Vibrio harveyi*, which infects mollusks, crustaceans, starfish, and fish (Bondad-Reantaso et al., 2023).

Phage-host interactions are complex, involving gene transfer and varying virulence, affecting genetic traits and relationships. Bacterial hosts can carry prophage-encoded virulence factors, altering virulence and enabling anti-virulence therapy (Defoirdt, 2014). Phage resistance can lead to resistant bacterial strains and increased phage genome size. Resistance to one phage can make bacteria sensitive to others, and some phages remain pathogenic. Some phages may have mutually beneficial relationships with their hosts. While phage therapies are promising alternatives to traditional treatments, more research is needed for widespread use (Żaczek et al., 2020).

The use of phages against *Lactococcus garvieae* was first introduced in Japan in 1999, and since then, various phages have been applied to control bacterial pathogens such as *Vibrio*, *Flavobacterium*, *Edwardsiella*, and *Aeromonas* species across different regions. A notable phage-based product, CuSTuS®, has been launched by ACD Pharmaceuticals in Norway, targeting *Yersinia ruckeri* in salmonids with considerable success. Similarly, Proteon Pharmaceuticals has introduced BAFADOR®, a phage cocktail that targets *Pseudomonas* and *Aeromonas* infections. These products exemplify the growing adoption and regulatory approval of phage therapy in aquaculture, particularly in Europe (Kalatzis, 2019).

Quorum Quenching

Quorum quenching (QQ) encompasses processes that inhibit quorum sensing (QS), which regulates gene expression by monitoring the density of the bacterial population. Many bacteria use QS signals to coordinate diverse behaviors through microorganism-microorganism interactions in various environments. Quorum quenching involves multiple phenomena and mechanisms, including enzymes, chemical compounds, and different mechanisms of action such as QS signal degradation and competitive inhibition. All major steps of the QS pathway can be affected, including synthesis, diffusion, and perception of QS signals. Therefore, QQ has been used for biocontrol of aquatic diseases (Grandclement et al., 2016).

Surface-attached bacteria form biofilms embedded in a hydrogel matrix, making them more resistant than planktonic forms and potentially more resistant to antibiotics. These biofilms interact with QS, a communication method that enables bacteria to communicate. QS uses signaling molecules called autoinducers, which are small, diffusible molecules. Autoinducers activate genes that control various functions such as biofilm formation, virulence, invasion, and dissemination. Blocking QS with QQ can potentially stop gene expression that controls virulence (Grandclément et al., 2016; Bondad-Reantaso et al., 2023).

Antimicrobial Peptides

Antimicrobial peptides (AMPs) are gaining attention in aquaculture as a sustainable alternative to antibiotics, particularly effective against drug-resistant pathogens. Derived from various natural sources such as bacteria, fungi, plants, and also vertebrates, AMPs disrupt cell membranes, making it difficult for pathogens to develop resistance. Fish, which are highly dependent on innate immunity, are significant sources of AMP. Although their application in aquaculture has not yet advanced due to production cost and stability problems, advances in synthetic peptide design may improve their feasibility (Pant et al., 2023).

Bacteriocins

Bacteriocins are bioactive compounds produced by bacteria and are suggested as antibiotic alternatives in aquaculture. These ribosome-synthesized, low-molecular-weight peptides (20-60 amino acids) are encoded in chromosomes or extrachromosomal elements. They have antimicrobial properties, inhibiting or killing various microorganisms.

Bacteriocins are environmentally friendly, biodegradable, non-harmful to hosts, antagonistic to harmful intestinal pathogens, and promote beneficial bacteria (Nayak et al., 2021).

Probiotics

Recent studies have indicated that aquaculture products' healthy and balanced gut microbiome reduces the risk of disease and stress in growing conditions by optimizing nutrient digestion (Diwan et al., 2021; Yilmaz et al., 2022). Disrupted microbiomes are often associated with disease states and scientists as biomarkers to identify pathological problems (Romero et al., 2014). Some types of bacteria are common in healthy animals, while other types increase significantly increase in infected animals. This suggests that the microbiota of diseased animals is more affected by environmental factors and stress, leading to difficulties in regulating the digestive microbiota. A healthy gut microbiome prevents diseases in host organisms, while its disruption can lead to the presence and infections. For example, higher densities of *Aeromonas* bacteria were observed in diseased fish compared to healthy fish, suggesting that a balanced microbiome inhibits the pathogenicity of *Aeromonas* (Li et al., 2016).

Probiotics are live, non-pathogenic microorganisms that positively impact microbiomes and are widely used and commercially available worldwide. They are used to improve microbial balance, especially in the gastrointestinal tract, and primarily consist of yeasts and bacteria such as *Lactobacillus* and *Bifidobacterium* species, often added to foods as dietary supplements (Diwan et al., 2021). Probiotics have been scientifically demonstrated to be effective in preventing and treating various medical conditions, especially in improving gut health. These beneficial microorganisms improve health by inhibiting harmful bacteria through various mechanisms. Probiotic effects in the intestines of aquatic animals occur through pathways such as inhibition of pathogen adhesion, production of antimicrobial components, modulation of the immune system, strengthening of barrier function and lowering of luminal pH. In particular, lowering intestinal pH can alter the host immune response by reducing the colonization and invasion of pathogens (Bondad-Reantaso et al., 2023).

Probiotics benefit aquatic animals by synthesizing essential nutrients like unsaturated fatty acids and vitamin B12 (Diwan et al., 2021). *Bacillus* probiotics also improve the environment by assimilating organic pollutants like ammonia and nitrites, reducing stress and toxicity. These probiotics also compete with opportunistic pathogens for access to nutrients, thus preventing the bacterial pathogens present in the same ecosystem from becoming harmful to aquaculture. This is especially true for many *Vibrio* species, which contribute significantly to the health of aquatic animals (Bondad-Reantaso et al., 2023).

Lactobacillus spp. and *Bacillus* spp. are the most commonly used probiotic species. *Lactobacillus* species help improve the gut flora in fish and optimize nutrient absorption by increasing digestive enzymes (Verschuere et al., 2000). Additionally, *Lactobacillus* species act as competitive inhibitors against pathogenic bacteria, contributing to disease prevention (Nayak, 2010). *Bacillus* spp. are robust spore-producing bacteria that can be added to fish feed. These bacteria establish themselves in the gut, preventing the proliferation of harmful bacteria and improving water quality (Moriarty, 1998). One of the most significant features of *Bacillus* species is their resistance to high temperatures and digestive processes, making them easily incorporated into feed formulations (Dawood et al., 2019). Other probiotics such as *Pediococcus* spp. and *Enterococcus* spp. are also used in aquaculture. These species modulate the immune system of fish, enhancing resistance to infections (Nikoskelainen et al., 2003). *Pediococcus* species are particularly effective in cold-water fish, helping to protect these fish from diseases even at low temperatures (Vendrell et al., 2008).

Prebiotics

Prebiotics are non-living food supplements, typically a family of carbohydrates consisting of oligosaccharides, that are generally not digested by the host but can be digested by certain populations of gut bacteria (Goh et al., 2022). These ingredients act as selective substrates for bacteria, specifically promoting the growth of beneficial gut bacteria. This modification causes specific changes of the intestinal flora, thereby improving the overall well-being and health of the host (Yilmaz et al., 2022).

Commonly used prebiotics in aquaculture include inulin, fructooligosaccharides (FOS), and mannan oligosaccharides (MOS). These compounds serve as substrates for beneficial microorganisms like *Bifidobacteria* and *Lactobacillus*, which can outcompete pathogenic bacteria in the gastrointestinal tract, leading to enhanced health and growth performance of aquatic species (Goh et al., 2022). For instance, inulin has been extensively studied for its effects on fish and shellfish. In turbot larvae, dietary inclusion of inulin has been shown to increase the relative mass of the gastrointestinal tract and promote the proliferation of beneficial *Bacillus* species, while concurrently reducing harmful *Vibrio* species (Mahious et al., 2006). Similarly, mannan oligosaccharides have been used to enhance the growth performance, feed efficiency, and immune responses in species such as rainbow trout and European sea bass. These prebiotics modulate the gut microbiota, leading to improved resistance against common pathogens like *Streptococcus* and *Mycobacterium* (Staykov et al., 2007; Torrecillas et al., 2007).

The beneficial effects of probiotic bacteria can be enhanced when used together with prebiotics and synbiotics. Synbiotics consist of a combination of probiotics and prebiotics, containing difficult-to-digest fibers that support the growth of beneficial commensal bacteria in the intestine. The beneficial effects provided by this combination arise from the by-products of the fermentation of commensal bacteria, which have the capacity to modulate the immune system. In particular, synbiotics can stimulate the immune systems of aquatic animals at both systemic and local levels through immunosaccharides (Diwan et al., 2021).

New research highlights the importance of parabiotics (dead probiotic cells) and postbiotics (probiotic culture supernatants) in the microbiome and disease formation (Goh et al., 2022). Metagenomic techniques and next-generation sequencing (NGS) now allow the identification of previously unculturable bacterial species, enhancing our understanding of microbiomes. This opens new research areas for antibiotic alternatives, better microbiome control, and improved health of aquatic organisms (Diwan et al., 2021).

Egg Yolk Immunoglobulin

Chicken egg yolk immunoglobulin (IgY) is a cost-effective antibody for passive immunization, produced in large quantities through chicken immunization. IgY has been successfully used in humans, livestock, and aquatic animals, offering greater stability than IgG (Baloch et al., 2015). It effectively controls various bacterial and viral pathogens in aquaculture, such as *Vibrio harveyi*, *V. anguillarum*, and *Aeromonas salmonicida* (Bondad-Reantaso et al., 2023). IgY can be administered by injection, immersion, or oral administration, providing passive immunity and enhancing resistance to disease in fish and shrimp (Gan et al., 2015; Winkelbach et al., 2015).

Nanoparticles

Nanoparticles are being used in aquaculture to address antibiotic issues by leveraging their production of reactive oxygen species to degrade antibiotics, thus mitigating pollution. For instance, titanium dioxide nanoparticles exhibit photocatalytic properties, killing a wide range of microorganisms including bacteria, fungi, and viruses (Foster et al., 2011). Furthermore, iron nanoparticles can break down toxic compounds in water, demonstrating the potential for antibiotic degradation (Majumder & Dash, 2017). This innovative approach improves the sustainability of aquaculture by reducing the use of traditional antibiotics (Fajardo et al., 2022).

Medicinal Plants

Medicinal plants and their derivatives have gained attention as antibiotic alternatives in aquaculture due to their low cost, ease of preparation, and minimal side effects (Tadese et al., 2022). These plants, including herbs, spices, seaweed, and traditional Chinese medicines, contain active ingredients such as polysaccharides, steroids, and secondary metabolites (Citarasu, 2010). They possess antimicrobial properties and stimulate both innate and specific immunity, increasing resistance to pathogens. Common immunostimulants derived from microbial cell walls include β-glucans, alginates, and polysaccharides, typically administered by bait or bath immersion (Harikrishnan et al., 2011; Tadese et al., 2022).

In recent years, a wide variety of medicinal plants have been studied for their effectiveness in aquaculture. For instance, *Euphorbia hirta* has been shown to improve resistance to *Aeromonas hydrophila* in sharptooth catfish (*Clarias gariepinus*) (Sheikhlar et al., 2017). *Ocimum sanctum*, commonly known as holy basil, has demonstrated immunostimulatory effects in *Oreochromis mossambicus*. Rosemary (*Rosmarinus officinalis*) has been used as a treatment against *Streptococcus iniae* in tilapia (*Oreochromis sp.*) (Abutbul et al., 2004; Tadese et al., 2022).

Furthermore, dietary administration of water hyacinth (*Eichhornia crassipes*) leaf extracts has been found to enhance innate immune parameters, antioxidant defense, and disease resistance in rainbow trout (*Oncorhynchus mykiss*) (Rufchaei et al., 2020). The use of *Coriandrum sativum* extract in diets has also shown positive effects on growth and immunity in fish (Farsani et al., 2019).

Recombinant Proteins

Recombinant proteins show great promise in combating infectious diseases in aquaculture (Mohammadzadeh et al., 2022). Recombinant hepcidin has demonstrated preventive and therapeutic effects against *Flavobacterium columnare* in grass carp by regulating iron distribution and immune gene expression (Wang et al., 2016). Another example is recombinant AHL-lactonase from *Bacillus sp.*, which reduced mortality in common carp infected with *Aeromonas hydrophila* (Chen et al., 2010). Additionally, a vibrio phage recombinant endolysin expressed in *E. coli* effectively lysed *Vibrio parahaemolyticus* (Melo-López et al., 2021).

Conclusion

Aquaculture has faced significant challenges in recent years, including disease outbreaks and antimicrobial resistance, threatening its sustainability. This situation requires the investigation of alternative antimicrobial strategies. Various methods have emerged as potential solutions. Vaccines, for example, play a crucial role in disease prevention and control, effectively reducing antibiotic use, as demonstrated in Norwegian salmon farming. However, vaccines are generally limited to valuable fish species due to high costs and logistical difficulties. Recent technological advances have made oral and immersion vaccines more viable, though further research on their effectiveness is needed. Biological solutions such as probiotics and prebiotics offer significant opportunities to increase disease resistance by supporting the health of the microbiome. These microorganisms enhance intestinal health and the overall well-being of aquatic animals. Innovative methods such as IgY provide passive immunity, while phage therapy targets bacterial pathogens without harming the environment. Natural products like herbal treatments and immunostimulants offer low-cost, environmentally friendly alternatives. Although these strategies present a holistic approach to prevention and control in aquaculture, their effectiveness varies depending on environmental conditions, species, and pathogen characteristics. Therefore, it is crucial to tailor strategies to local ecosystem needs, recognizing that these methods work synergistically and require continuous development and adaptation. Integrating the most effective and sustainable methods, while considering the risks, limitations, and potential benefits of each strategy, is critical for the future of aquaculture.

Compliance With Ethical Standards

Authors' Contributions

NK: Conceptualization, Writing – original draft, Writing – review and editing, Supervision

GG: Writing – original draft, Data curation, Visualization

All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest.

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For this type of study, formal consent is not required.

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